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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/593,518	05/22/2007	Tomoyuki Nishikawa	29473-013 NATL	9089

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EXAMINER	
STOICA, ELLY GERALD	

ART UNIT	PAPER NUMBER
1647	

MAIL DATE	DELIVERY MODE
04/15/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/593,518	NISHIKAWA ET AL.	
	Examiner	Art Unit	
	ELLY-GERALD STOICA	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18,20-26 and 39-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18,20-26 and 39-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/05/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. In the amendment submitted on 02/13/2009, Applicant cancelled claims 1-17, 19, 27-38 and added the new claims 39-46. Currently, claims 18, 20-26 and 39-46 are pending and examined.

Withdrawn claim rejections

2. The rejections of claims 18-23 under 35 U.S.C. 101 is withdrawn in view of the amendments to the claims.

3. The rejections of claims 18-23 under 35 U.S.C. 102(b) is withdrawn in view of the amendments to the claims. Specifically, Applicant introduced functional language and limited the claimed polypeptide as encoded by the polynucleotide sequence consisting of SEQ ID NO: 1.

New and maintained claim rejections necessitated by amendment

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 20 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the claims contains the recitation "wherein the polynucleotide comprises a peptide". It unclear how a polynucleotide may *comprise* a

peptide and thus the metes and bounds of the claim could not be determined. Changing the word "comprises" to "encodes" would be remedial.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 42-46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The independent claim 42 is drawn to a genus of polypeptides consisting of the amino acid sequence of SEQ ID NO: 2 or a fragment thereof.

While the structure of the polypeptide of SEQ ID NO 2 is described and its properties disclosed, the specification also describes a "fragment" as to a polypeptide or polynucleotide having a sequence length of from 1 to n-1 relative to a full-length polypeptide or polynucleotide (whose length is n). The length of a fragment can be changed depending on the object, and the lower limit of a polypeptide for example is a length of 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50 or more amino acids, and a length expressed by an integer not specifically enumerated herein (for example, or the like) can also be suitable as the lower limit. The lower limit of a polynucleotide is a length of 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 75, 100 or more nucleotides, and a length expressed by an integer not specifically enumerated herein can also be suitable as the

lower limit (p. 15, lines 12-24). Thus, according to this description, even a single amino acid is envisioned as being encompassed by the claims.

Thus, the claims are drawn to a genus of proteins that is defined only by partial sequence identity which would not indicate which part of the molecule is to be conserved for the functionality of the protein.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of a fragment of polypeptide. There is no identification of any particular portion of the structure that must be conserved in order to preserve functionality.

Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. Additionally, the description of one polypeptide species (SEQ ID NO: 2) is not adequate written description of an entire genus of functionally equivalent polypeptides which incorporate all fragments with unknown functionality.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the

'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

With the exception of the SEQ ID NO:2 the skilled artisan cannot envision the detailed chemical structure of the encompassed proteins, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Therefore, only the polypeptide of SEQ ID NO: 2, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

8. Claims 20, 21 and 42-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polypeptide of SEQ ID NO: 2 that has the vascular endothelial cell growth activity and angiogenesis activity does not reasonably provide enablement for a fragment that has the specified activities or for the polypeptide and the fragment having an activity in promoting transcription from c-fos promoter or an activity in promoting transcription from VEGF promoter. The specification does not enable any person skilled in the art to which it pertains, or with

which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are drawn to a protein of SEQ ID NO: 2 or a fragment of it wherein the polypeptide has an activity selected from the group consisting of a vascular endothelial cell growth activity, activity in promoting transcription from c-fos promoter, activity in promoting transcription from VEGF promoter, and angiogenesis activity.

The specification provides the functional limitation of a peptide of the Invention as having at least one activity selected from vascular endothelial cell growth activity, activity in promoting transcription from c-fos promoter, activity in promoting transcription from VEGF promoter and angiogenesis activity (p. 10, lines 15-20). The structural limitations were presented supra and, as detailed there, there is no adequate written description of the peptide claimed beyond the SEQ ID NO: 2. The specification does not teach fragments of the peptide other than the full-length of SEQ ID NO: 2. The specification also does not teach functional or structural characteristics of the fragments.

The problem of predicting protein and DNA structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and DNA is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495;- all cited previously). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the DNA and protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from

structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427- all cited previously).

The working examples provided include only the peptide of SEQ ID NO: 2 and there is nothing in the specification that would indicate that a fragment of this peptide could be used in the procedures in which the peptide of SEQ ID NO: 2 was used. The unpredictability of the art is *very high* with regards to undisclosed variants of the peptide that would be able to have the effects claimed. It would also necessitate a great amount of experimentation and functional testing, both in vitro and in vivo, first to obtain the fragments of the peptide of SEQ ID NO: 2.

With regard to the activity of the polypeptide of SEQ ID NO 2, the specification does not present any working examples or guidance with respect to the polypeptide having any of the following activities: an activity in promoting transcription from c-fos promoter or an activity in promoting transcription from VEGF promoter. The art is unaware of such properties for peptides having VEGF activities and the amount of experimentation to test such improbable activities is considerable

Due to the large quantity of experimentation necessary to generate the undisclosed number of fragments recited in the claims and possibly screen the same for known activities and also to test the polypeptide of SEQ ID NO 2 for the unknown in the art activities claimed; the lack of direction/guidance presented in the specification

regarding which structural features are required in order to provide activity; the absence of working examples directed to same; the complex nature of the invention; the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function and the unpredictability of the new activities claimed for the polypeptides of SEQ ID NO 2; and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and use the claimed invention in its full scope.

Conclusion

9. Claims 18, 25, 26, 39-41 are allowed. Claims 22-24 would be allowable if written in a form that is not dependent on the rejected claim 21. Claims 20, 21, and 42-46 are not allowed.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ELLY-GERALD STOICA whose telephone number is (571)272-9941. The examiner can normally be reached on 9:00-18:30 M-Th and 9:00-18:30 alternate F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christine J Saoud/
Primary Examiner, Art Unit 1647